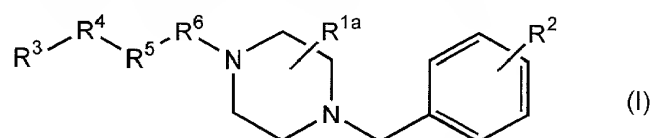


What is claimed is:

1. A pharmaceutical composition useful in treating heart transplant rejection in mammals, which composition comprises one or more pharmaceutically acceptable excipients, a therapeutically effective amount of a non-peptide CCR1 receptor antagonist and a sub-nephrotoxic amount of cyclosporin A.

2. The pharmaceutical composition of Claim 1 wherein the non-peptide CCR1 receptor antagonist is a compound selected from formula (I):



wherein:

R^{1a} is one or more substituents independently selected from the group consisting of alkyl or hydroxyalkyl;

R² is fluoro at the 4-position;

R³ is phenyl substituted at the 4-position with chloro and at the 2-position by aminocarbonyl, ureido or glycinamido;

R⁴ is -O-;

R⁵ is methylene; and

R⁶ is -C(O)-;

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of Claim 2 wherein the non-peptide CCR1 receptor antagonist is selected from the group consisting of:

(2*R*,5*S*)-1-((4-chloro-2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

and

(2*R*,5*S*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

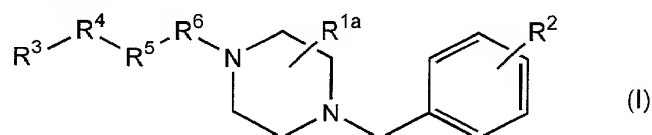
4. The pharmaceutical composition of Claim 2 wherein the non-peptide CCR1 receptor antagonist is (2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine.

5. The pharmaceutical composition of Claim 4 wherein the mammal in need thereof is a human.

6. A method of administering to a mammal in need thereof a pharmaceutical composition useful in treating heart transplant rejection in mammals, which composition comprises a one or more pharmaceutically acceptable excipients, a therapeutically effective amount of a non-peptide CCR1 receptor antagonist and a sub-nephrotoxic amount of cyclosporin A.

7. The method of Claim 6 wherein the non-peptide CCR1 receptor antagonist and the cyclosporin A are administered to the mammal in need thereof simultaneously or sequentially.

8. The method of Claim 7 wherein the non-peptide CCR1 receptor antagonist is a compound selected from formula (I):



wherein:

R^{1a} is one or more substituents independently selected from the group consisting of alkyl or hydroxyalkyl;

R² is fluoro at the 4-position;

R³ is phenyl substituted at the 4-position with chloro and at the 2-position by aminocarbonyl, ureido or glycinamido;

R⁴ is -O-;

R⁵ is methylene; and

R⁶ is -C(O)-;

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

9. The method of Claim 8 wherein the non-peptide CCR1 receptor antagonist is selected from the group consisting of:

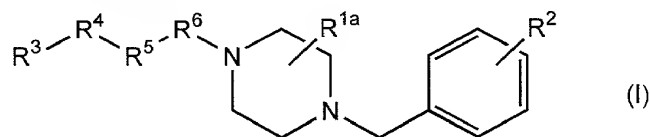
- (2*R*,5*S*)-1-((4-chloro-2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;
 (*trans*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;
 (2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;
 (*trans*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;
 (2*R*,5*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;
 and
 (2*R*,5*S*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

10. The method of Claim 8 wherein the non-peptide CCR1 receptor antagonist is (2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine.

11. The method of Claim 8 wherein the mammal in need thereof is a human.

12. A method of treating heart transplant rejection in a mammal which method comprises administering to a mammal in need thereof a pharmaceutical composition comprising one or more pharmaceutically acceptable excipients, a therapeutically effective amount of a non-peptide CCR1 receptor antagonist and a sub-nephrotoxic amount of cyclosporin A.

13. The method of Claim 12 wherein the non-peptide CCR1 receptor antagonist is a compound selected from formula (I):



wherein:

R^{1a} is one or more substituents independently selected from the group consisting of alkyl or hydroxyalkyl;

R² is fluoro at the 4-position;

R³ is phenyl substituted at the 4-position with chloro and at the 2-position by aminocarbonyl, ureido or glycinamido;

R⁴ is -O-;

R⁵ is methylene; and

R⁶ is -C(O)-;

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

14. The method of Claim 13 wherein the non-peptide CCR1 receptor antagonist is selected from the group consisting of:

(2*R*,5*S*)-1-((4-chloro-2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;
and

(2*R*,5*S*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

15. The method of Claim 13 wherein the non-peptide CCR1 receptor antagonist is (2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine.

16. The method of Claim 15 wherein the mammal in need thereof is a human.

17. The method of Claim 15 wherein the non-peptide CCR1 receptor antagonist and the cyclosporin A are administered to the mammal in need thereof simultaneously or sequentially.